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X-Linked Mental Retardation Syndrome: Three Brothers With the Brooks-Wisniewski-Brown Syndrome

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We report on 3 brothers with growth and mental retardation, bifrontal narrowness, short palpebral fissures, deeply set eyes with entropion, wide bulbous nose, small mouth, myopia, and spastic diplegia. The patients were born to normal and non-consanguineous parents. The similarity of our cases with those recently reported by Brooks et al. [Am J Med Genet 51:586–590, 1994] supports their suggestion that these patients are representative of a distinct entity. © 1996 Wiley-Liss, Inc.

KEY WORDS: X-linked mental retardation, new syndrome, deeply set eyes, short palpebral fissures, entropion, wide nose tip, small mouth

INTRODUCTION

Recently, Brooks et al. [1994] described a family with an apparent X-linked recessive form of mental retardation (XLMR) syndrome characterized by a distinct facial appearance, growth retardation, severe mental retardation, spastic diplegia, ocular findings, and atrophic hydrocephalus. They postulated that their patients may represent a new XLMR syndrome. Here we report on a non-consanguineous couple whose 3 sons had an almost identical clinical picture with particularly similar facial appearance. This syndrome seems to be a distinct form of XLMR out of the more than 50 different forms described so far [Neri et al., 1994].

CLINICAL REPORTS

Patient 1

The family was investigated through the 2 sibs (patients 2 and 3) still alive in 1995. Pedigree analysis showed a deceased older brother (patient 1) who was the first child of healthy, non-consanguineous parents after an induced abortion. He was born at term with a birthweight of 2,800 g after an uneventful pregnancy. No perinatal problems were noted. His growth was delayed. At the age of 4 years, his weight was 6,900 g (−5 SD), length 85 cm (−4 SD), head circumference 44 cm (−5 SD). On a picture taken by the parents at the age of 6 months (Fig. 1), bifrontal narrowness, deeply set eyes, short palpebral fissures, wide nose tip, small mouth, and low hairline can be seen. According to the medical records, he also had limited movement at the knees and elbows, mild optic atrophy, and myopia. He was followed up since the age of 6 months because of seizures. The ultrasound examination of the head demonstrated a moderate internal hydrocephalus. On EEG, generalized paroxysmal discharges were found. He had spastic diplegia, decreased muscle strength, tone, and bulk. His psychomotor development was profoundly retarded. He could not sit and was non-verbal. He died at the age of 4 years during an episode of respiratory tract infection.

Patient 2

Patient 2 was born from the fifth uneventful pregnancy after two spontaneous abortions when the mother was 24 and the father 25 years old. He was born at 36 gestational weeks with a birthweight of 2,720 g by induced delivery because of rupture of the membranes associated with maternal fever. He had hyperbilirubinaemia. Neurological examination at the age of 1 year showed profound psychomotor retardation, generalized hypotonia, and he could only turn over. He became progressively more dystrophic.

When examined at 3 years (Fig. 2), he could not sit, his psychomotor development was that of an 8.5-month-old, length 77 cm (−4.5 SD), weight 7,300 g (−4.5 SD), head circumference 44 cm (−4.5 SD). Deeply set eyes and almond shaped palpebral fissures were noted. The inner canthal distance was 2.4 cm (−1 SD), the outer canthal distance 7.1 cm (−4 SD). He had epicanthus and a remarkable entropion of the lower lids. Myopia was of 2.5 D on both eyes. Philtrum length was 0.9 cm (3rd–25th centile). He had a triangular face, bifrontal narrowness, low hairline, full medial eyebrows, wide nose tip, low-set ears, small mouth with thin upper lip, and malar flatness. There was limited extension at the left elbow, mild pectus excavatum, and clinodactyly of the 5 fingers. He had hypotonic cerebral

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Fig. 1. Patient 1 on a family picture at the age of 6 months. Note bifrontal narrowness, deeply set eyes, wide nose, and small mouth.

palsy with decreased muscle strength and muscle wasting. There was also a tendency to hypertonicity with deLange sign (crossing of lower limbs).

Cranial ultrasound and MRI examinations showed ventricular enlargement and corpus callosum dysgenesis. EEG was normal. Results of chromosome examination including fragile X analysis were normal.

Patient 3

Patient 3, the youngest brother, was born at term 2 years later with a birthweight of 2,600 g. He could turn over by the age of 6 months. Since the age of 10 months, he has been on anticonvulsive medication because of episodes of tonic-clonic jerks and abnormal EEG. When examined at the age of 1 year (Fig. 3), he could not sit. His length was 74 cm (mean), weight 7,100 g (−3 SD) and head circumference 42 cm (−3 SD). Except for a rounded shape, his face and facial anomalies were strikingly similar to those of his brothers (Table I). Inner canthal distance was 2.1 cm (−2 SD) and outer canthal distance 7.2 cm (−6 SD). The philtrum length was 0.95 cm (P25). Myopia (2.0 D, 1.75 D) was also found. No joint contractures were found, and pectus excavatum was mild. Neurological examination at the age of 1 year showed generalized hypotonia with spasticity in the lower limbs. He did not react to noises and sounds and did not try to reach for objects. He gave no sounds, only cried.

Fig. 2. Facial appearance of patient 2.

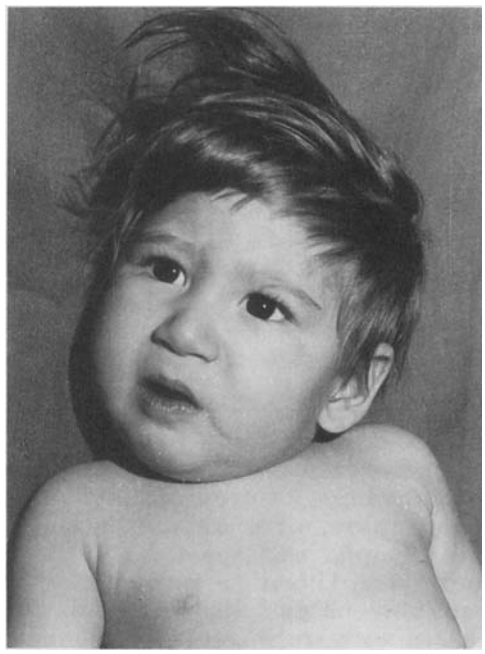

Fig. 3. Facial appearance of patient 3.

Ultrasound examination of the head did not show any abnormalities. Laboratory tests including karyotype analysis and fragile X test were normal. On BERA examination, reactions for signals could be detected only to 60 DB and 80 DB on the right and left side, respectively.

DISCUSSION

The constellation and the remarkable similarity of the signs and symptoms of the 3 reported sibs and the lack of abnormalities of the parents are suggestive of a distinct syndrome with recessive inheritance. The fact that all 3 sibs were boys suggests the possibility of an XLMR syndrome.

In a recent review, Neri et al. [1994] provided a comprehensive list of all known forms of X-linked mental retardation, altogether 127 entries, including 57 clinically recognisable syndromes. Although some of these conditions overlap with the syndrome of our patients, none but one fits in acceptably. Hamel et al. [1994] reported on four male relatives with mental retardation who share with our patients the short stature, narrow face, malar flatness, and bulbous nose. However, they additionally had congenital heart defect and cleft palate. The patients of Prieto et al. [1987] and those of Stoll et al. [1991] had hypertelorism, a finding absent in our cases. Patients of Zollino et al. [1992] had a large mouth and short anteverted nose, in addition to a char-

TABLE I. Summary of Clinical Findings in Present and Literature Patients

	Present patients			Brooks et al. [1994] patients
	1	2	3	
Measurements				
Birth weight (g)	2,800	2,720	2,600	
Age at examination (yr)	n.a.[a]	3	1	
Height (length, cm)	–	77	74	
Weight (g)	–	7,300	7,100	
Head circumference (cm)	–	44	42	
Inner canthal distance (cm)	–	2.4	2.1	
Outer canthal distance (cm)	–	7.1	6.2	
Craniofacial signs				
Triangular face	+	+	–	2/3
Bifrontal narrowness	+	+	+	3/3
Low hairline	+	+	+	3/3
Malar flatness	+	+	+	3/3
Entropion/epicanthus inversus	+	+	+	3/3
Short palpebral fissures	n.m.[b]	+	+	2/3
Deeply set eyes	+	+	+	3/3
Full medial eyebrows	+	+	+	2/3
Wide/bulbous nose tip	+	+	+	3/3
Malposition of ears	–	+	+	2/3
Small mouth	+	+	+	3/3
Thin upper lip	+	+	–	2/3
Skeletal				
Knee/elbow contractures	+	Mild	–	2/3
Pectus excavatum	–	Mild	Mild	3/3
Clinodactyly of the 5th finger	–	+	+	2/3
Neurological				
Psychomotor retardation	Profound	Profound	Increasing	3/3
Spastic diplegia	+	+	+	3/3
Enlarged ventricles	+	+	–	3/3
Corpus callosum dysgenesis	–	+	–	1/3
Seizures	+	–	+	0/3
Myopia	+	+	+	3/3
Optic atrophy	Mild	–	–	2/3

[a] n.a. = not applicable.
[b] n.m. = not measured.

acteristic pachygyria. More significantly, none of the above-mentioned cases referred to had short palpebral fissures, entropion, and small mouth, and none of the central nervous system signs and symptoms that our patients had. The cases of Kang et al. [1992] also had hypertelorism. However, the mid-facial region of these patients of Chinese origin is difficult to compare with that of our patients.

On the other hand, striking similarities were found between our 3 patients and those described by Brooks et al. [1994] in a recent report. All of 6 patients shared, with minor variation, a most characteristic combination of bifrontal narrowness, low hairline, deeply set eyes with epicanthus, small palpebral fissures, entropion of the lower eyelids, and bulbous tip of the nose; all had somatic growth delay, severe to profound developmental and mental retardation, myopia, and spastic diplegia (Table I). All 3 cases of Brooks et al. [1994] and 2 of ours had enlarged cerebral ventricles. Relative small mouth, a finding not mentioned by Brooks et al. [1994] but identifiable on the pictures of their patients, contributes to a characteristic face.

There are also some differences between the two sibships compared. The boys of Brooks et al. [1994] were markedly small for gestational age which was not significant in our cases. Two of our 3 sibs had seizure disorder that was not present in cases of Brooks et al. [1994]. Our patients had less expressed pectus excavatum, joint contractures, and optic atrophy, although these abnormalities may be age-dependent, a fact that has to be taken into account when comparing our patients, who are younger, with those of Brooks et al. [1994]. Nevertheless, the phenotypic similarity of the 6 cases is more impressive than the differences, which suggests that all are representative of the same entity.

The patients reported by Smith et al. [1980] had rather similar facial appearance as our patients, and the possibility that they also represent the same entity cannot be excluded.

As most characteristic in this likely distinct entity, we emphasize the constellation of bifrontal narrowness, low hairline, deeply set eyes with entropion/epicanthus inversus and short palpebral fissures, wide and bulbous tip of the nose, and relatively small mouth.

When these anomalies can be found in a boy with otherwise unidentified mental retardation, severe developmental delay and/or cerebral palsy, this XLMR syndrome should be considered.

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